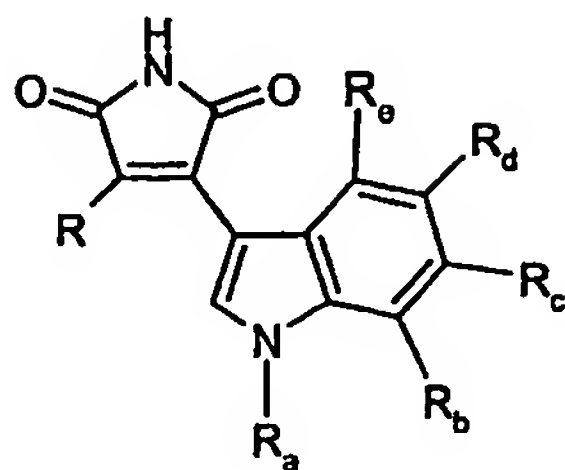


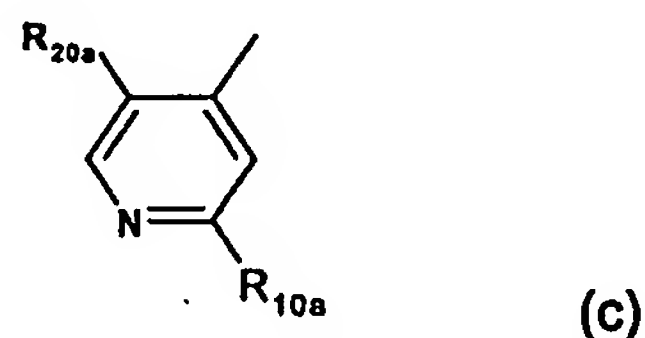
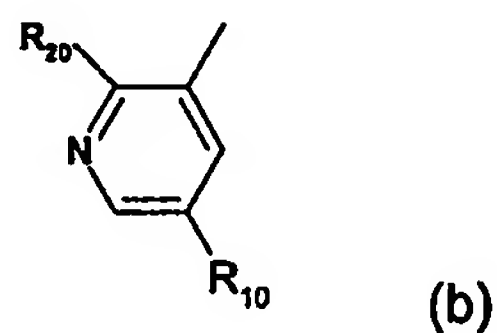
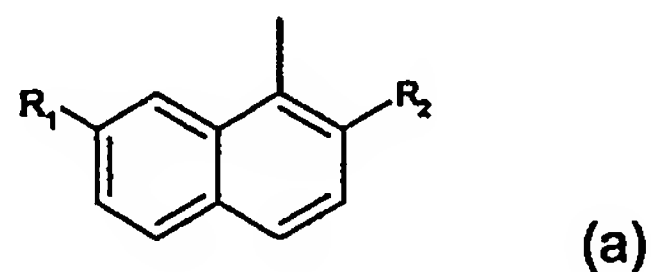
CLAIMS

1. Use of a compound which is an inhibitor of PKC, in free form or in a pharmaceutically acceptable salt form, for the manufacture of a medicament for treating or preventing diseases or disorders mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer, wherein said compound possesses a selectivity for PKC α , PKC β and optionally PKC θ , over one or more of the other PKC isoforms of at least 10 fold, as measured by the ratio of the IC₅₀ of the compound for a PKC which is not α and β , and optionally not θ , to the IC₅₀ of the compound for the PKC α , PKC β or PKC θ , respectively.
2. A compound which is an inhibitor of the PKC, in free form or in a pharmaceutically acceptable salt form, wherein said compound possesses a selectivity for the PKC over one or more protein kinases which do not belong to the CDK-family, and a selectivity for the PKC α , PKC β and optionally PKC θ , over one or more of the other PKC isoforms of at least 10 fold, as measured according to claim 1.
3. A compound which is an inhibitor of the PKC, in free form or in a pharmaceutically acceptable salt form, wherein said compound possesses a selectivity for PKC α , PKC β and optionally PKC θ , over one or more of the other PKC isoforms of at least 10 fold, and for which the ratio of the IC₅₀ value as determined by Allogeneic Mixed Lymphocyte Reaction (MLR) assay to the IC₅₀ value as determined by Bone Marrow proliferative (BM) assay is higher than 5.
4. A compound which is an inhibitor of the PKC, in free form or in a pharmaceutically acceptable salt form, wherein said compound possesses a selectivity for the PKC α , PKC β and PKC θ , over one or more of the other PKC isoforms of at least 10 fold, as measured according to claim 1.
5. A compound of formula I



wherein

R_a is H; C_{1-4} alkyl; or C_{1-4} alkyl substituted by OH, NH_2 , NHC_{1-4} alkyl or $N(di-C_{1-4}alkyl)_2$;
 one of R_b , R_c , R_d and R_e is halogen; C_{1-4} alkoxy; C_{1-4} alkyl; CF_3 or CN and the other three substituents are each H; or R_b , R_c , R_d and R_e are all H; and
 R is a radical of formula (a), (b) or (c)



wherein

R_1 is $-(CH_2)_n-NR_3R_4$,

wherein

each of R_3 and R_4 , independently, is H or C_{1-4} alkyl; or R_3 and R_4 form together with the nitrogen atom to which they are bound a heterocyclic residue;

n is 0, 1 or 2; and

R_2 is H; halogen; C_{1-4} alkyl; CF_3 ; OH; SH; NH_2 ; C_{1-4} alkoxy; C_{1-4} alkylthio; NHC_{1-4} alkyl; $N(di-C_{1-4}alkyl)_2$, CN, alkyne or NO_2 ;

wherein

each of R_{10} and R_{10a} , independently, is a heterocyclic residue; or a radical of formula α



wherein X is a direct bond, O, S or NR₁₁ wherein R₁₁ is H or C₁₋₄alkyl,

R_f is C₁₋₄alkylene or C₁₋₄alkylene wherein one CH₂ is replaced by CR_xR_y wherein one of R_x and R_y is H and the other is CH₃, each of R_x and R_y is CH₃ or R_x and R_y form together -CH₂-CH₂-,

Y is bound to the terminal carbon atom and is selected from OH, -NR₃₀R₄₀ wherein each of R₃₀ and R₄₀, independently, is H, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, aryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl, C₂₋₆alkenyl or C₁₋₄alkyl optionally substituted on the terminal carbon atom by OH, halogen, C₁₋₄alkoxy or -NR₅₀R₆₀ wherein each of R₅₀ and R₆₀, independently, is H, C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, aryl-C₁₋₄alkyl, or R₃₀ and R₄₀ form together with the nitrogen atom to which they are bound a heterocyclic residue; and

each of R₂₀ and R_{20a}, independently, is H; halogen; C₁₋₄alkyl; C₁₋₄alkoxy; CF₃; nitrile; nitro or amino;

or a salt thereof.

6. A compound according to claim 5 wherein R_a is H or methyl; each of R₂, R₂₀ and R_{20a}, independently, is H, Cl, NO₂, F, CF₃ or methyl, n is 0 or 1; one of R_b, R_c, R_d and R_e is methyl or ethyl and the other three substituents are H; or R_b, R_c, R_d and R_e are all H; and each of R₃ and R₄, independently, is H, methyl, ethyl or *i*-propyl; or R₃ and R₄ form together with the nitrogen atom to which they are bound a heterocyclic residue optionally substituted; and each of R₁, R₁₀ and R_{10a}, independently, is a heterocyclic residue.

7. A compound according to claim 5 or 6 which is selected from

3-[5-Chloro-2-(4-methyl-piperazin-1-yl)-pyridin-4-yl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-Chloro-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(6-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(5-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(6-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(5-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-{2-Chloro-7-[(ethyl-methyl-amino)-methyl]-naphthalen-1-yl}-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-diethylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-ethylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-[2-Chloro-7-(isopropylamino-methyl)-naphthalen-1-yl]-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-[2-Chloro-7-(4-methyl-piperazin-1-ylmethyl) naphthalen-1-yl]-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-pyrrolidin-1-ylmethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(1,7-dimethyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-naphthalen-1-yl)-4-(1-H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Amino-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Amino-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Dimethylaminomethyl-2-fluoro-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-dimethylaminomethyl-2-fluoro-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(1-Methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrrole-2,5-dione;

3-(1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrrole-2,5-dione;

3-(7-methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-pyridin-3-yl]-pyrrole-2,5-dione;
3-(1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-pyridin-3-yl]-pyrrole-2,5-dione;
3-(1-methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-pyridin-3-yl]-pyrrole-2,5-dione;
3-(7-methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrrole-2,5-dione;
3-(1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-nitro-pyridin-3-yl]-pyrrole-2,5-dione;
3-[2-chloro-5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;
3-(1H-indol-3-yl)-4-[5-methyl-2-(4-methyl-piperazin-1-yl)-pyridin-4-yl]-pyrrole-2,5-dione;
3-(1H-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-5-nitro-pyridin-4-yl]-pyrrole-2,5-dione;
3-(1H-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-pyridin-4-yl]-pyrrole-2,5-dione; in free form or in a pharmaceutically acceptable salt form.

8. A compound according to any one of claims 5 to 7, in free form or in a pharmaceutically acceptable salt form, for use as a pharmaceutical.

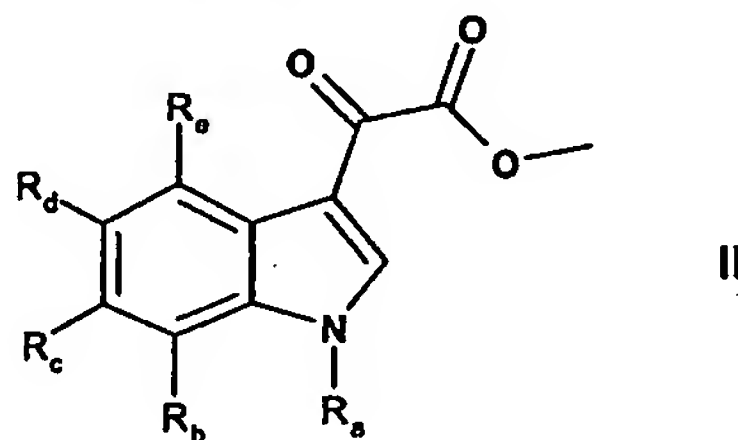
9. A compound according to any one of claims 2 to 7, for treating or preventing diseases or disorders mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer.

10. A pharmaceutical composition comprising a compound according to any one of claims 2 to 7, in free form or in pharmaceutically acceptable salt form, in association with a pharmaceutically acceptable diluent or carrier therefor.

11. Use of a compound according to any one of claims 2 to 7, in free form or in a pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for treating or preventing diseases or disorders mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer.

12. A pharmaceutical combination comprising a compound according to any one of claims 2 to 7, in free form or in a pharmaceutically acceptable salt form, and a further agent selected from immunosuppressant, immunomodulatory, anti-inflammatory, chemotherapeutic, antiproliferative and anti-diabetic agents.

13. A process for the production of a compound according to claim 5 or 6, which process comprises reacting a compound of formula II



wherein R_a to R_e are as defined in claim 5,

with a compound of formula III



wherein R is as defined in claim 5,

and, where required, converting the resulting compound of formula I obtained in free form to a salt form or vice versa, as appropriate.

14. A method for treating or preventing disorders or diseases mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of an inhibitor of PKC which possesses a selectivity for $PKC\alpha$, $PKC\beta$ and optionally $PKC\theta$, over one or more of the other PKC isoforms of at least 10 fold, as measured according to claim 1, or a pharmaceutically acceptable salt thereof.

17. A method for treating or preventing disorders or diseases mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of a compound according to any one of claims 2 to 7, or a pharmaceutically acceptable salt thereof.